Remarks

Claims 1-9, 12-14, 18, 20-23, 25, 26 and 33 are pending in this application. Claims 1, 13 and 14 have been amended. Support for claim amendments can be found throughout the specification including page 22, lines 15-29 and the claims as originally filed. No new matter is introduced by these amendments.

After entry of this amendment **claims 1, 9, 12-14, 18, 20-23, 25, 26 and 33 are pending in this application**.

Interview with Examiner Kim

Applicants thank Examiner Kim for discussing the pending Office action with their undersigned representative on March 3, 2009. During this interview, the mode of administration of a drug combination comprising neostigmine and glycopyrrolate in regards to the newly cited art Casadio (0140434 A2) was discussed as well as the difference between chronic and acute bowel obstruction. In particular, Applicants' representative stated that none of the references either alone or in combination taught the present bowel care method. Applicants' representative also stated that chronic and acute bowel obstruction are very dissimilar conditions and require different treatment regimes. Due to these differences, Applicants' representative argued that one of ordinary skill in the art would not have predicted that such agents could be used to treat chronic pseudo obstruction (chronic constipation). Examiner Kim suggested that evidence in the form of scientific publications or patents be presented to support such position.

Although an agreement was not reached, Examiner Kim agreed to consider Applicants arguments, amendments and evidence presented herewith. It is believed that this response is prepared in accordance with suggestions made by Examiner Kim.

Claim Rejections under 35 U.S.C. §112, second paragraph:

Claims 13 and 14 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for providing insufficient antecedent basis for the terms "acetylcholinesterase

inhibitor" and "anti-cholinerigic agent." Claims 13 and 14 are amended herein to remove these terms, thereby rending the rejection moot.

Claim Rejections under 35 U.S.C. §103:

Claims 1, 9, 12-14, 20-23, 25, 26 and 33 were rejected under 35 U.S.C. §103 as allegedly being obvious in light of Ponec *et al.* (*New England J. Med.* 341(3): 137-141, 1999; hereinafter Ponec *et al.*) in view of Vavilala *et al.* (*New England J. Med.* 341(21): 137, 1999; hereinafter Vavilala *et al.*) and further in view of Casadio (EP 0140434 A2; hereinafter referred to as Casadio). Applicants traverse this rejection for at least the following reasons.

Ponec *et al.* disclose intravenous administration of neostigmine for the treatment of acute colonic pseudo-obstruction. Acute colonic pseudo-obstruction is massive dilation of the colon without mechanical obstruction that occurs following surgery or acute illness. Ponec *et al.* teach that a side effect of the administration of neostigmine is bradycardia.

Vavilala *et al.* teach that because bradycardia is a complication of neostigmine therapy, another antimuscarinic agent can be administered, such as glycopyrrolate, to minimize bradycardia. Vavilala *et al.* disclose using glycopyrrolate with continuous monitoring by electrocardiography and blood pressure assessment following neostigmine administration in the acute setting of the operating room.

Casadio discloses a pharmaceutical composition suitable for nasal administration that includes a therapeutically active dose of a parasympathomimetic quaternary ammonium salt. In particular, Casadio teach that the parasympathomimetic quaternary ammonium salts can be neostigmine methylsulphate or glycopyrronium bromide.

To establish a *prima facie* case of obviousness, the Examiner must identify all of the claimed elements in one or more prior art references and provide a motivation or suggestion to combine or modify the prior art references coupled with a reasonable expectation of success (MPEP §2143).

Cited References Fail to Teach all of the Claimed Elements

The Office has failed to establish a *prima facie* case of obviousness because all of the claim elements are not taught, suggested or disclosed by the cited references. At best, Ponec *et al.* in view of Vavilala *et al.* teach intravenous administration of neostigmine and glycopyrrolate to treat acute colonic pseudo-obstruction with continuous monitoring including simultaneous electrocardiography and blood pressure assessment. Neither Ponec *et al.* or Vavilala *et al.* disclose, suggest or render obvious "a method of bowel care comprising chronically administering intra-nasally a therapeutically effective amount of a drug combination comprising neostigmine and glycopyrrolate to a subject having chronic intestinal pseudo-obstruction to relieve chronic constipation, wherein the chronic intestinal pseudo-obstruction is a result of spinal cord injury and the ratio of neostigmine to glycopyrrolate is 2.5:1 to 10:1 by weight, thereby achieving bowel evacuation events without substantial bradycardia on a scheduled basis over a period of at least two weeks" as presently required by the claims. Ponec *et al.* and Vavilala *et al.* teach the use of drugs in the acute setting, they most certainly do not teach administration over at least two weeks (claim 1), one month (claims 20, 22, and 23) or six months (claims 21 and 26).

The Office relies upon Casadio for allegedly teaching intranasal administration of neostigmine and glycopyrrolate (Office action, page 4; citing claims 1-7, particularly claims 2 and 7). In particular, the Examiner alleges that "Casadio teaches a pharmaceutical composition comprising neostigmine and glycopyrronium bromide (glycopyrrolate) with a nasal carrier which are suitable to be administered as intranasal formulations" (*Id*). However, a review of the cited claims reveals that Casadio does not disclose administration of a composition including neostigmine and glycopyrrolate, but, instead discloses compositions including either neostigmine or glycopyrronium bromide and an intranasal carrier. Further, nowhere in Casadio is it suggested that these two compounds could be co-administered intranasally as presently claimed. Additionally, Casadio does not teach the use of intranasal administration of neostigmine or glycopyrronium bromide for treatment of chronic constipation. Therefore, none of the references either alone or in combination teach a method of bowel care as presently claimed, which require intranasal administration of neostigmine and glycopyrrolate at a therapeutically effective concentration for the treatment of chronic constipation. Because the references cited by the

Examiner fail to teach or suggest all of the elements of the claims, such references cannot serve as the basis of a rejection of the claims under 35 U.S.C. §103(a).

One of Skill in the Art Could Not Have Predicted That Prior Art Could Have Been Modified with Reasonable Expectation of Success

Chronic intestinal pseudo-obstruction is a very different condition from acute intestinal pseudo-obstruction. Acute intestinal pseudo-obstruction is "a relatively rapid onset, intense, short-term occurrence of intestinal pseudo-obstruction" (see the specification at page 13, lines 4-9). Indeed, acute pseudo-obstruction is a condition that has a rapid onset, and can be a life threatening condition associated with abdominal pain and distension, inability to eat, electrolyte abnormalities and the need for immediate intervention. As defined by Ponec *et al.*, "acute colonic pseudo-obstruction consists of massive dilation of the colon in the absence of mechanical obstruction" (Ponec *et al.*, page 137, column 2, lines 1-3). Chronic intestinal pseudo-obstruction, however, is "persistent, recurring intestinal pseudo-obstruction" (see the specification at page 13, lines 9-10). The inability to eliminate stool from the colon after spinal cord injury is characterized by long-term difficulty with stool evacuation and/or fecal incontinence that results in a chronic problem that may last for many years. Thus, acute pseudo-obstruction and chronic pseudo-obstruction are very dissimilar conditions, with very different etiologies.

Not only are acute pseudo-obstruction and chronic pseudo-obstruction very different conditions, the traditional treatment regimes for such conditions are also very distinct. As stated above, Ponec *et al.* and Vavilala *et al.* teach intravenous administration of neostigmine and glycopyrrolate to treat acute colonic pseudo-obstruction with continuous monitoring including simultaneous electrocardiography and blood pressure assessment. Nowhere does either of these references suggest the use of such compounds to treat chronic pseudo- obstruction to relieve constipation. Casadio also does not suggest the use of intranasal administration of neostigmine or glycopyrronium bromide for treatment of chronic constipation. A review of the scientific literature reveals that generally accepted chronic constipation treatments involve non-pharmacological approaches (such as increasing fiber in diet, increasing physical activity, or cognitive behavior therapy) as well as pharmacological approaches (such as polyethylene glycol,

stimulant laxatives, chloride channel activators, 5-HT4 agonists, or probiotics). (See Foxx-Orenstein *et al.*, *Cleveland Clinic Journal of Medicine* 75(11): 813-824, 2008; Gallagher *et al.*, *Drugs Aging* 25(10): 807-821, 2008; Pohl *et al.*, *Current Opinion in Pharmacology* 8: 724-728, 2008; and Singal *et al.*, *Advances in Medical Sciences* 51: 15-22, 2006 all provided herewith in Appendix A). None of these could possibly be efficacious in the acute setting, such as in the operating room. Therefore, absent Applicants' disclosure of a method of bowel care including "chronically administering intra-nasally a therapeutically effective amount of a drug combination comprising neostigmine and glycopyrrolate to a subject having chronic intestinal pseudo-obstruction to relieve chronic constipation", one of ordinary skill in the art would not reasonably believe that such method could be used on a chronic basis.

Similarly, there are very dramatic treatments of use in the operating room that would never be applied in the chronic setting. For example, to treat blood loss in the acute setting, a massive blood transfusion could be administered. However, massive transfusions would not be administered in a chronic setting, such as for treating mild anemia, a less invasive method of treatment could be chosen. Indeed, the known "toxicity" of cholinergic agents in persons with spinal cord injury teaches away from the use of neostigmine in a chronic setting (See Guttman and Walsh *Paraplegia* 1: 39-50, 1971; Chapelle *et al.*, *Paraplegia* 21: 30-36, 1983; Radulovic *et al.*, *Journal of Rehabilitation Research and Development*, 41: 63-58, 2004 all provided herewith in Appendix A and supported by Dr. Marino's Declaration submitted herewith). Guttman and Walsh as well as Chapelle *et al.* discuss a number of the risks involved with providing an anticholinergic agent to a subject with a spinal cord injury. In particular, Guttman and Walsh disclose that administration of prostigmin to a male patient with a spinal cord injury can lead to death (pages 47 and 48). Prostigmin is a cholinergic agent that readily crosses the blood brain barrier, unlike neostigmine. However, in prior studies, neostigmine had been administered by lumbar puncture to permit its action on the central nervous system. Thus, the references can be construed to suggest that any cholinergic agent would produce similar toxic consequences on the nervous system and therefore, would not be used to treat day to day bowel care problems. As such, it is clear that treatments used in the chronic and acute settings are vastly different.

Submitted herewith is a Declaration from Dr. Ralph Marino a full-time academic physician at Thomas Jefferson Hospital who specializes in patients with spinal cord injuries and has been practicing in the field of rehabilitation medicine since 1988. Dr. Marino's states that a practicing physician at the time the application was filed, would not believe that neostigmine in combination with glycopyrrolate could be used to treat constipation in patients with spinal cord injuries. He confirms that the clinical practical guidelines for treating constipation do not include administration of neostigmine. Instead, he provides documentation that chronic constipation is treated by non-pharmacological approaches (such as increasing fiber in diet, increasing physical activity, or cognitive behavior therapy) as well as pharmacological approaches (such as polyethylene glycol or stimulant laxatives). (See Foxx-Orenstein *et al.*, *Cleveland Clinic Journal of Medicine* 75(11): 813-824, 2008; Gallagher *et al.*, *Drugs Aging* 25(10): 807-821, 2008; Pohl *et al.*, *Current Opinion in Pharmacology* 8: 724-728, 2008; and Singal *et al.*, *Advances in Medical Sciences* 51: 15-22, 2006 as provided in Appendix A). Dr. Marino acknowledges the known risks associated providing anticholinergic agents to subjects with spinal cord injuries.

The cited art specifies that the composition is to be used to treat acute pseudo-obstruction and administered intravenously, under closely monitored conditions. From these teachings, those provided in Appendix A and the Declaration provided by Dr. Ralph Marino, one of ordinary skill in the art would not have had a reasonable expectation of success of using the drug combination in a chronic setting without the continuous monitoring. As such, a *prima facie* case of obviousness has not been established because one of ordinary skill in the art could not have reasonably predicted that the claimed method could have been used to treat chronic constipation with a reasonable expectation of success.

Based on all of the foregoing arguments and evidence submitted herewith, Applicants request that the §103 rejection of these claims be withdrawn.

CONCLUSION

Based on the foregoing amendments, arguments and evidence submitted herewith, the claims are in condition for allowance and notification to this effect is requested. If for any

reason the Examiner believes that a telephone conference would expedite allowance of these claims, please telephone the undersigned at (503) 595-5300.

Respectfully submitted,

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